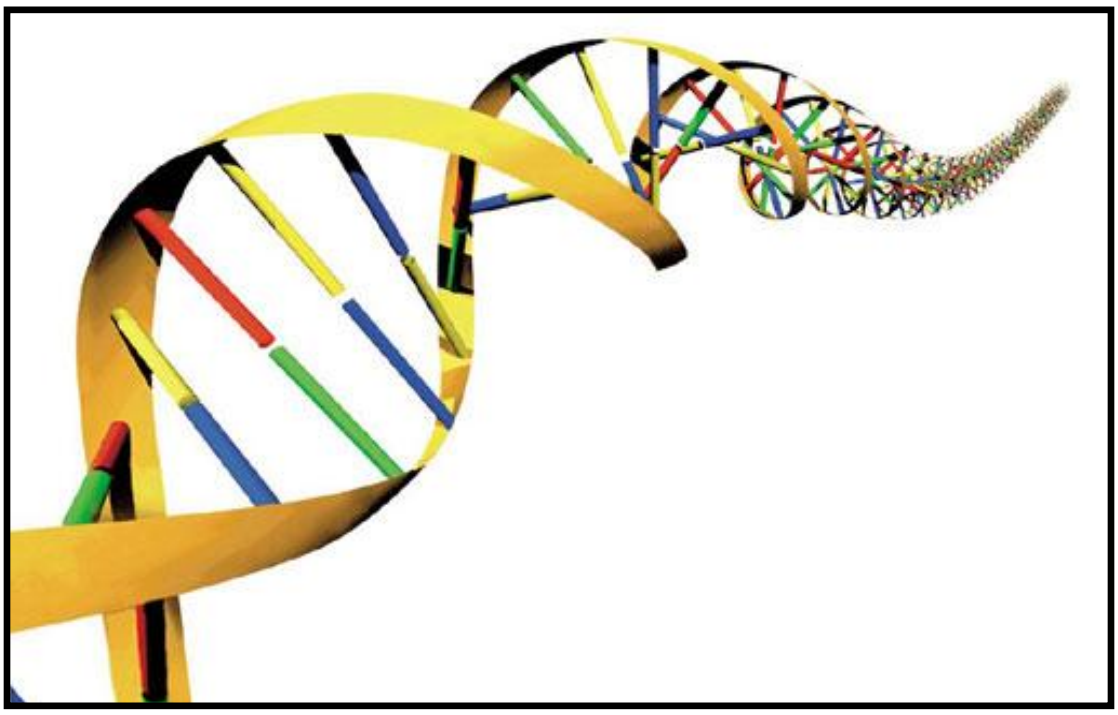
Important notes in

Molecular Biology

for first year medical students



presented by

bio chemistry
different view

إهداء

إلى طلبة وطالبات الفرقة الأولى

أقدم لكم مراجعة سريعة وشاملة للـ Molecular Biology

حاولت فيها مراعاة كتابة كل النقاط التى تصلح لنظام الـ MCQs

وهى لن تغنى عن مذاكرة المنهج جيدا ،
ولكنها علامات مضيئة فى مذاكرتك الأيام المقبلة

وأنصحكم بالآتي :

1- مذاكرة المنهج من كتاب القسم و فهم كل النقاط بشكل إجمالي
2- قراءة ملزمة المراجعة وحفظ النقاط التى بها
3- إجابة أسئلة الـ MCQs الموجودة فى كتاب الأسئلة الخاص بالقسم

نسأل الله عز وجل أن يتقبل منكم جهدكم فى المذاكرة ، وأن يوفقكم فى امتحانات نصف العام

ولا تنسونا من صالح دعائكم
مع تمنياتى لكم بالنجاح والتوفيق

د. هيثم

Nucleotide chemistry

- Pyrimidine bases :- uracil(in RNA), thymine(In DNA) & cytosine.
- Purine bases:- guanine & adenine
- Tautomers :-
  1- Adenine & cytosine form amino or imino (mostly amino).
  2- Guanine & thymine form keto or enol (mostly keto).

- Anti-conformation:the nucleotide & base are not in the same side to glycosidic bond.(the predominant)
- Syn-conformation: the nucleotide & base are in the same side to glycosidic bond.
- Phosphodiester bond :- 3' to 5' between two nucleotide
- Nucleoside :- nitrogenous base & pentose sugar
- Nucleotide :- nitrogenous base & pentose sugar & phosphate
- **Importance of nucleic acids :**
  1- DNA or RNA.
  2- High energy sources ,e.g. ATP.
  3- Coenzymes:- FAD , NAD.
  4- Regulatory function :- 2ry messenger cAMP .
  5- Activation methyl group :-s-adenosyl methionine
  6- Important intermediates UDP-glucose
  7- Synthetic analogues
     - ✓ Anti-tumor :- 5-flurouracil , 6-mercaptopurine.
     - ✓ Antiviral agent:- AZT for HIV.
     - ✓ TTT of gout :- allopurinol inhibit xanthine oxidase.

من كتاب " مفتاح النجاح " لدكتور عائض القرني

- بارك الله لأمتي في بكورها، فإذا أردت عملاً فعليك بالصباح فإنه أسعد الأوقات.
- لا تقف، فإن الملائكة تكتب، والعمر ينصرم، والموت قادم، وكل نَفَسٍ يخرج لن يعود.
- مـ ـــن زرع (سـ ـــوفَ) أنبتـ ـــتْ لـ ـــه (لعـ ـــل) وأطلعـ ـــت (بعسـ ـــى) وأثمـ ـــرت (بليت) لها طعم الندامة ومذاق الحسرة.

DNA structure

- DNA is polar due to it has phosphate at 5'end & (OH) 3' end.
- Chargaff rule & base complementarity (A=T) 2 H bond, (G≡C)3 H bond.
- Waston Crick double helix model (B-form)
  - ✓ Right handed double helix
    (hydrophilic deoxyribose-P outside)(hydrophobic base inside)
  - ✓ Antiparallei
  - ✓ 10 base pair per turn
  - ✓ Minor & major groove.
- Staking interaction by (hydrogen bond & hydrophobic interaction)
- Denaturation of DNA 1- Change in pH. 2- heating
- A-T base-paires is less stable than G-C
- Melting temperature™:- point ay which 50% of DNA molecule exists as single strand.
- Z-form :- Lt handed helix ,zigzag , 12 bp\turn
- A-form:- Rt handed helix,11 bp\turn. Not found in nature.
- Human genome:- total DNA of chromosomes in a cell
- Histones
  - ✓ 5 different types(H1,H2A,H2B,H3,H4)
  - ✓ Rich in basic amino acids arginine & lysine
  - ✓ Nucleosome:- octamer protein(H2A,H2B,H3,H4)+DNA
  - ✓ H1 present in between nucleosome . linker coromosomes.

- إذا أصبحت فلا تنتظر المساء، وبادر الفرصة، وأحذر البغتة، وإياك والتأجيل والتردد، وإذا عزمـت فتوكـل على الله.
- الإبداع إن تجيد في تخصصك ، وما يناسب مواهبك، فقد علم كل أناس مشربهم، ولكل وجهة هو موليها.
- لا يضير الناجحين كلام الساقطين، فإنه علو ورفعة
- الناجح يقوم بمشاريع يعجز عنها الخيال، وتبهر عظماء الرجال، وتثير الدهشـة والغرابـة والتعجـب مـن عظمتها.
- الناجح لا يعيش على هامش الأحداث، ولا يكون صفراً بلا قيمة، ولا زيادة في حاشية.

Replication

- Central dogma is flow of formation for DNA to RNA to protein.
- DNA replication is **semiconsevative** manner.(each daughter contain parent DNA & new one.)
- **Ori C** is the origin of replication in prokaryotes, **ARS** in eukatyotes (many origin of replication "AT base pair")
- **Prepriming complex** composed of :-
  1- Dna A protein recognize origin of replication &separate small region by ATP hydrolysis.
  2- Helicase enzyme separate double helix by cleavage of hydrogen bonds.(need ATP)
  3- (SSB) bind single strand prevent repairimg & protect from nucleases
- Topoisomerase has nuclease & ligase activity to solve supercoils.

Topoisomerase I	Topoisomerase II
cut one strand	Cut two strands
Not need ATP	Need ATP

- DNA gyrase : is type II topoisomerase present in bacterio make –Ve supercoils.
- DNA replications is bidirectional.
- Polymerases
  1- Cannot initiate DNA synthesis (need primer)
  2- use deoxynucleoside triphosphate then release PPi
  3- only from 5' to 3' (read DNA template from 3' to 5')
- **primosome** complex is prepriming complex + primase.
- Leading strand is formed continuousily & need one primer (follow helicase & replication fork)
- Lagging strand dis continuousily & need many primer (opposite helicase & replication fork)
- Fragment formed in lagging strand are called Okazaki fragments.
- Polymerase I has three activities :-
  1- Polymerase 5' to 3' : replace primer
  2- Exonuclease from 3' to 5' : proof reading activity
  3- Exonuclease from 5' to 3' :remove primer & repair (difference from 3' to 5')

Feature (prokatyotes)	Pol I	Pol II	Pol III
Exonuclease from 5' to 3'	+	--	--
Exonuclease from 3' to 5'	+	+	+
Rate of synthesis	600	30	30000
Replication	+	--	+
repair	+	?	+

- Eukaryotic replication :-
  1- Multiple origin
  2- RNase H remove primer
  3- occur only in S phase
  4- check points (cyclins)

Polymerase (eukaryotes)	function	Proof reading
Pol α	Primase &polymerase	No
Pol β	Repair	No
Pol γ	Replicate mitochondrial DNA	Yes
Pol δ	Replication	Yes
Pol ε	Repair	yes

- Tolemers :-DNA-protein complex at end of chromosome (to solve problem of 5’ end in lagging strands)
- Tolemers is biologic clock for cell
- Tolemerase in germ , stem & cancer cells (contain reverse transcriptase & short piece of RNA).

- إن الماء الراكد يأسن، وإن البلبل المحبوس يموت، والليث المقيد يذل.
- قيل لأبي مسلم الخرساني: مالك لا تنام ؟ قال: همة عارمة، وعزيمة ماضية، ونفس لا تقبل الضيم .
- أجرى أديسون مكتشف الكهرباء عشرة آلاف تجربة على بطارية، كلها أخطأت فواصل حتى نجح.
- وأقام أنشتاين عمره كله في النظرية النسبية.
- جمِع من براية أقلام ابن الجوزي ما أُدفِئ به ماء غسله عند الموت.
- الذي يقهر نفسه أعظم ممن يفتح مدينة، والذي يقاوم هواه أجل ممن يحارب جيشاً.
- صام أبو طلحة الأنصاري أربعين سنة سرداً ، وحج ابن المسيب ستين حجة، وأفتى الإمام أحمد في ستين ألف مسألة بالدليل.

DNA repair

- If there is no repair this cause
  1- Apoptosis: programmed cell death.
  2- Malignant tumor due to unrepaired lesion in tumor suppressor genes

A- Repair of thymine dimmer :- (formed by UV rays & prevent replication)

a- Direct repair (photo reactivation):-
In bacteria visible light → (+) photolyase → reverse damage.

b- Nucleotide-excision repair :- (mainly in human)

1- UVr-ABC exinuclease :-made to cuts in DNA to remove short oligonucleotide that contain dimmer (12 in bacteria , 29 in human)

2- DNA polymerase (I in bacteria , ε in human), DNA ligase .

B- Base excision repair : remove &repair the defective base only

1- DNA glycosylase : remove abnormal base to create AP site (cleaveN- glycosidic bond)
2- AP endonucleases : cut phosphodiester bond at 5' end of AP site
3- AP lyase : remove the single empty sugar phosphate
4- DNA polymerase I.
5- Ligase.

C- Methyl directed repair (mismatch repair):

Identification by Mut protein (S,H,L) to new strand (non methylated)
Endonuclease (Mut H) **>>** Helicase & Exonuclease **>>** DNA polymerase I **>>** Ligase.

- Hereditary nopolyposis colorectal cancer is due to mutation in proteins of mismatch repair.
- Xeroderma pigmentosum (**XP**): defect in nucleotide excision repair gene lead to skin cancers.

RNA structure

- RNA are destroyed by alkali & contain intrastrand H-bonds,
- but DNA is resistant & contain H-bonds between two strands.

1- m RNA (messenger) **5%** of the total RNA
- exons :- coding regions
- Introns:- untranslated region in-between exons
- untranslated region in both 5'&3' end (UTRs) regulatory regions
- 5' end is 7-methylguanosine cap
- 3' end contain poly A tail.

2- r RNA (ribosomal) **80 %** of total RNA
@ prokaryotes (23S , 16S , 5S) @ eukaryotes (28S , 18S , 5.8S , 5S)

3- t RNA (transfer) adaptors (contain anticodon) **15%** of total RNA
- has CCA at 3' end (amino acids binding site)
- has 4 single stranded loops
- has modified bases.
- Contain intra-chain H-bonds (cloverleaf shape).

Transcription

- Template strand (antisense) :- the strand that will be transcribed
- Coding strand (sense):- the other strand
- Promoter :-
  1- Specific sequence on DNA that recognized to initiate RNA synthesis at specific point
  2- Upstream to the template strand, near the gene that will be transcribed.
- Prokaryotic RNA polymerase:- (holoenzyme)
  1- Core enzyme : 4 subunit (2 α, 1β,1β') responsible for 5' to 3' polymerase activity
  2- The σ sigma subunit :- recognize promoter region
  3- Ω ohm subunit :- unclear function.
- Eukaryotic RNA polymerase :

name	Product
RNA POL I	Larger ribosomal RNA (28S,18S,5.8S)
RNA POL II	mRNA & snRNA
RNA POL III	tRNA & small ribosomal RNA (5S)

- **Initiation in prokaryotes:-**
  - ✓ Prinbow box or TATA box :- (-10),TATAAT,absolutely essential for transcription
  - ✓ TG box :- (-35),TTGACA, allow very high transcription rate .
  - ✓ Closed complex :- holoenzyme + double strand DNA.
- **Initiation in eukaryotes:-**
  - ✓ Basal eukaryotic transcription complex :- RNA polymerase + transcription factor.
  - ✓ Hogness box :- TATAAA, bind to transcription factor (promoter).
  - ✓ CAAT box :- CACGGTG, regulatory sequences.
- **Regulation of transcription in eukaryotes**
  - **1- Chromosomal remodeling**
    - **a-** *Histone acetylation\deacetylation:-*
      Acetylation of lysine in histones eliminate +ve charge & decrease interaction with DNA.
      Acetylation made by histone acetyltransferase,&removed by deacetylases
    - **b-** *DNA methylation :-*
      Methylation of cytosine residues in 5-carbon position
      Prevent binding of transcription factors to promoter
      Made by methyl transferase
      Methylation induce histone deacetylation
  - **2- Cis-acting element (DNA sequences)**
    a- Silencers :- bind with repressor to decrease rate of transcription.
    b- Enhancers:- bind to factors to increase rate of transcription.
  - **3- Trans acting elements (regulatory proteins)**
    a- Repressor :- bind with silencer to decrease rate of transcription
    b - Inducer :- bind with repressor to detach it & increase rate of transcription.

- Open complex: - holoenzyme + single strand DNA.
- Elongation cannot proceed until sigma factor dissociate from enzyme.
- Most transcripts originate using purine nucleotide triphosphate (GTP & ATP).
- **Termination in prokaryotes:-**

1- Rho –independent termination (intrinsic factor):-

- ✓ Loop structure (palindromic sequence rich in G-C inverted repeated)
- ✓ Poly A sequence (due to repeated T in DNA).

2- Rho –dependent termination :-

- ✓ ATP dependent.
- ✓ Need Rho protein.

- Post transcription modification :-
  1- rRNA form subunits
  2- tRNA processing (cleave the original transcript by ribonucleases)
  - ✓ remove introns
  - ✓ add CCA to 3' terminal
  - ✓ modification of some bases

  3- mRNA
  - ✓ heterogenous nuclear RNA:- precursor of mRNA.
  - ✓ 5' capping
  - ✓ Addition of poly A tail,by polyadenylate polymerase,use ATP as a substrate.
  - ✓ Remove introns(splicing) by (snRNA &protein)(snRNP)
  - ✓ Systemic lupus erythromatosis due to autoimmune response toward snRNP.
  - ✓ Alternative slicing produce proteins with different activity e.g. tropomyosin ,Igs

- Reverse transcriptase :- produce DNA from RNA
  (In prokaryotes ,e.g. HIV) (in eukaryotes e.g. telomerase)
- Ribonuclease H digest RNA strand
- integrase enzyme introduce complementary DNA into human cells

عن عبد الله بن مسعود رضي الله عنه قال:
سألت النبي صلى الله عليه وسلم أي العمل أحب إلى الله عز وجل؟
قال: (الصلاة على وقتها)
قال: ثم أي؟
قال: (بر الوالدين)
قال ثم أي؟
قال :(الجهاد في سبيل الله)

Genetic code

- Nonsense codons (termination codons) are tree in number, start codon only one.
- Degeneracy :- multiple codons decode the same amino acid (usually change is in the third base)
- Degeneracy decrease possibility of additional of abnormal AA with mutation in third base.
- Wobble hypothesis:-mechanism allow one tRNA to recognize more than one codon for AA.
- Unambiguous: code is specific (code fore one AA only).
- Neither overlapping nor punctuation in mRNA.
- Universal : all organisms use the same codes (with some exeptions)
- Mutation :

	A- Point mutation	B- Frame shift mutation
definition	Alter one base only	Add or delete one or two nucleutide
Types	**Transition**:-from purine to purine or pyrimidine to pyrimidine. **Transversion**:-from purine to pyrimidine & vise versa	
effect	1- Silent mutation (no effect,same amino acid) 2- Missense (other amino acid) (acceptable,partial or not) 3- Nonsense (termination code)	1- Premature termination 2- Altering the reading frame

- Cystic fibrosis(CF)
  - ✓ Affect lung & digestive system
  - ✓ Deletion of three nucleutides (for phenylalanine),prevent normal folding of CF transmembrane regulator (CFTR)
  - ✓ CFTR normally function as CL channel in epithelium
- Huntington disease
  - ✓ Amplification of CAG (glutamine) in Huntington protein.
  - ✓ Become unstable & accumulate cause neurodegenerative disorders
- Splice site mutation (e.g. β-thalassemia)

Translation

- If one amino acid is missed , transalation stops at the codon of this amino acids.
- Charged (t RNA) :- t RNA covalently attached to amino acid.(amino acid is activated).
- Codon & anticodon are complementary & anti parallel.
- Aminoacyl - t RNA synthetase :

  1- amino acid + ATP → aminoacyl-AMP + PP_i

  2- aminoacyl-AMP + tRNA → aminoacyl-tRNA + AMP

  ✓ 20 different Aminoacyl - t RNA synthetase present (one for each amino acid).
  ✓ Highly specific has proofreading activity .
  ✓ The formation of one Aminoacyl - t RNA needs 2 high energy phosphate bonds.

- Ribose (large & small unit)
  ✓ Prokaryotes (50S & 30S)(together 70S) ------ Eukaryotes (60S & 40S)(together 80).
  1- **A site :** bind to amino acyl-t RNA .
  2- **P site :** contain peptidyl t RNA .
  3- **E site :** empty t RNA to exit.
  ✓ Types
    1- Free ribosome :- synthesize proteins present in cell
    2- Membrane bounded ribosomes :- synthesize proteins that will be secreted or present in lysosome or gogi membrane .
    3- Polysomes :-intensive protein synthesis (several ribosome translate one mRNA)

- Transalation synthesize protein from amino terminal to carboxyl terminal .
- Polycistronic (prokaryotic m RNA contain several coding region)
- Monocistronic(eukaryotic m RNA contain one coding region).
- Difference in initiation between eukaryotes & prokaryotes :

Aspect	eukaryotes	prokaryotes
Binding of m RNA to small ribosomal subunit	Cap at 5' end of mRNA binds eIFs and 40S containing $tRNA^{met}$, mRNA is scanned for AUG start codon	Shine-Dalgarno sequence upstream to AUG bind to small ribosomal unit (16S)
Firist amino acid	methionine	Formyl-methionine
Initiation factors	eIFs(12 or more)	IFs (3)

- Peptidyltransferase form peptide bond (present in large subunit).
- Termination occurs by release factor(RF) when ribosome reace one of the termination codons.

- Regulation of translation :
  1- Covalent modification of eIF2 (phpsphorylated eIF2 is inactive) (in eukaryotes)
  2- Protein bind mRNA either inhibit or increase translation (in eukaryotes & prokaryotes).

- Four high energy bonds is required for addition of one amino acid intransalation
  - Two from ATP in aminoacyl-tRNA synthetase.
  - Two from GTP,one for binding of aminoacyl-tRNA to A site<and one for tranlocation
  - Formation of peptide bonds not need energy

- In eukaryotes (additional ATP & GTP are required for initiation).
- IN eukaryotes & prokaryotes (additional GTP for termination).
- For 100 residue protein, we need 400 energy.

جاء في الصحيحين عن أنس بن مالك - رضي الله عنه - أن رسول الله - صلى الله عليه وسلم - قال :
((ثلاث من كن فيه وجد حلاوة الإيمان ، أن يكون الله ورسوله أحب إليه مما سواهما ، وأن يحب المرء لا يحبه إلا لله ، وأن يكره أن يعود في الكفر كما يكره أن يقذف في النار)) .
قال الإمام الغزالي : " وكمال الحب أن يحب العبد ربه عز وجل بكل قلبه ، وما دام يلتفت إلى غيره فزاوية من قلبه مشغولة بغيره " .
أفاد الإمام ابن القيم في كتابه الداء والدواء أن المحبوب قسمان : محبوب لنفسه، ومحبوب لغيره ..وكل ما سوى المحبوب الحق فهو محبوب لغيره ، وليس شيء يحب لذاته إلا الله وحده ؛ لأنه سبحانه المتفرد بالكمال المطلق والجمال التام ، وكل ما سواه هو تبع لمحبته سبحانه كمحبة الملائكة والأنبياء والأولياء ، التي هي لازمة لمحبة الله عز وجل ؛ لأن محبته توجب محبة من يحبه فحب الله تعالى هو أعلى أنواع الحب .

Post translation

- Protein folding occurs co-translationally .
- Any mutation of any amino acid result in problems in folding
- Folding occur to make hydrophobic amino acids inside protein & hydrophilic amino acids in the surface.
- **Chaperones** :- (protect the protein from misfolding)
  1- De novo protein folding
  2- Stabilize proteins under stress (high temperature)(classified as heat shock protein)
  3- Maintain polypeptide chain in a loosely manner for translocation across organelles.
- **Misfolding**
  1- Alzheimer disease
    - ✓ Accumulation of misfolded protein called amyloid precursor protein(APP)
    - ✓ APP is degraded to form beta-amyloid that form plaques around neurons.
    - ✓ Loss of connection between nerve cells & brain

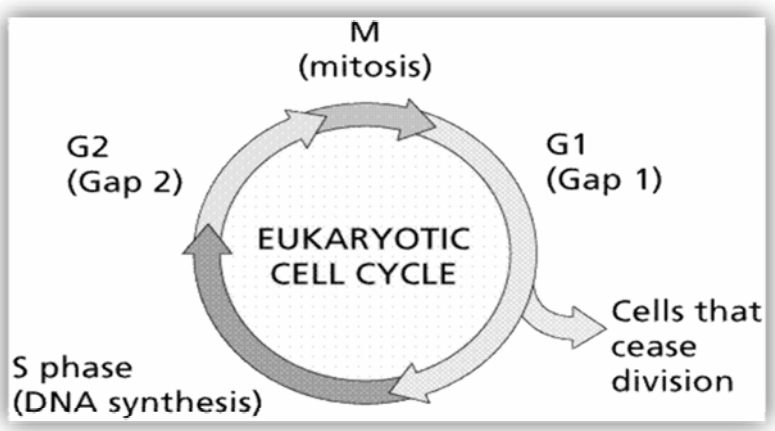
  2- Prion disease
    - ✓ Occur in human & animals
    - ✓ Create microscopic spong like holes in brain

  3- Alpha 1 antitrypsin deficiency
    - ✓ Accumulation in lung & liver
    - ✓ Elastase will destroy lung tissue & decrease elasticity
    - ✓ Cause emphysema in lung.
- **Post translation modification of polypeptide chains**
  a- Trimming :-remove part by endoproteases to make protein active. E.g. (insulin & zymogens)
  b- Covalent alteration
    1- Phosphorylation :-in (OH) of amino acids in enzymes to increase or decrease activity.
    2- Glycosylation :- in (OH) of amino acids & amide occur in golgi &(ER) to target protein.
    3- hydroxylation :- proline & lysine in collagen
    (for maximizing interchain H bonds & stabilizing trible helical structure)
- **Protein degredation :**- by ubiquitin made isopeptide bond by carboxyl of it & epsilon amino in lysine to be degraded in proteosome.

كان ابن تيميه إذا صعبت عليه مسألة استغفر ألف مرة، وقال تلاميذ الخطيب البغدادي له ـ وهم في سفر ـ حدثنا، فقال: نبدأ بالقرآن، فختمه كله ثم حدثهم.

important notes in MCQs

- Adenosine is the nucleoside of adenine
- Adenylic acid is the nucleotide of adenine (adenosine phosphate)
- The sugar of DNA is 5'-deoxyribose, sugar of RNA is ribose
- DNA strand in not branched.
- Denaturation of DNA (melting) (heating) disrupts hydrogen bonds.
- Denaturation increase DNA absorbance at 260 nm.
- RNA is not absolutely single strand (tRNA contain double strands)
- Okazaki fragments are not in leading strand (only in lagging).
- mRNA has the greatest sequence diversity between RNAs in cell
- retroviruses have reverse transcriptase
- the cap in mRNA is important to protect from nuclease & initiation of translation.
- Post transcription modification in which there is added sequence (mRNA & tRNA)
- Amino acid binds to CCA of tRNA by ester bond.
- Activator is the factor that control initiation of transcription.
- Non sense codon are not identical in nucleus & mitochondria.
- in polysome ,ribosome synthesizes the longest peptide chain is the nearest to 3'end of mRNA.
- Translocation in translation need EF & GTP



تصحيح بعض الإجابات الخاطئة فى كتاب القسم

Chapter 4	1 (d)					
Chapter 5	11 (all exceptزود على السؤال)	32 (b)				
Chapter 7	5 (b)	6 (e)	7 (c)	8 (b)	9 (a)	10 (d)

- Complete course in biochemistry for first year medical students.
- You can easily understand and study biochemistry.

: bio_differentview@hotmail.com

لمزيد من الإستفسارات
سنتر المستقبل : 10 ش مستشفى الدمرداش ت/ 0166714987